Workshop on Heritable Cancer Syndromes and Genetic Testing

Supplement to ***Cancer***

Genetic Counseling and Hereditary Cancer

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Genetic counseling is a communication process that deals with the psychologic, medical, and genetic issues associated with the occurrence or risk of occurrence of a genetic disorder within a family. It is practiced primarily by teams of medical geneticists working in conjunction with genetic counselors who have Master's degrees or higher.[1] It has previously been associated primarily with prenatal diagnosis and pediatric genetics services. Until recently, few genetic counselors have worked in adult genetics settings such as oncology. The genetic counseling profession has existed for 25 years and has produced approximately 1500 Master's level counselors.[2] These genetic counselors provide a rich service that addresses psychologic, social, ethical, and genetic concerns.[3] Generally, they have training not only in genetic principles but also in short term psychotherapeutic strategies.[4] Counselors strive to provide nondirective counseling services in an attempt to preserve clients' rights to make autonomous decisions.[5,6] They also provide supportive counseling to those who already have an affected child or family member.

Genetic counseling is sometimes compared with discussions with patients about genetic conditions, which occur in many medical settings. Most physicians and nurses provide some amount of genetic information in response to their patients' queries, but this is in sharp contrast to the lengthy process of assessing and addressing hereditary risks in an individual or family as carried out by trained, dedicated genetic professionals. Yet, despite the extensive clinical care and commitment that genetic counselors give their clients, there remain many unknowns about the effectiveness and efficacy of genetic counseling.[7] It is a new and relatively small clinical field, and there has been no formative research of the practice itself. There is a great need to determine the most effective strategies for addressing clients' needs.

Common Misunderstandings about Genetic Counseling

There are three commonly expressed misunderstandings about genetic counseling. The first is that it involves only the provision of risk information. Although many concur that giving information is an important component of genetic counseling, the counseling is not merely genetics education. It is narrow to think of risk as statistical risk only. The concept of risk really incorporates all of an individual's personal, emotional, social, and cultural values, beliefs, and attitudes, such that statistics cannot be isolated from an interpretation of the meaning of that statistic for a given person at a particular phase of the person's life narrative.[8] Superimposed on this are the difficulties that a layperson may have in understanding abstract laws of probability, inaccuracies that can result when an average population risk is applied to an individual whose personal risk may in fact be much

higher or lower than the average, preconceived notions about whether or not a particular person will be affected, and the tendency to simplify ambiguous risks into simple binary categories that will resolve uncertainties about outcome.[9]

Most clients have questions about why a condition has occurred in their family, but there are different ways to address the question, ''Why did this happen?'' Some individuals who ask this are expressing a more existential concern, such as, ''Why did this happen to me?'' or ''What did I do to deserve this?'' rather than requesting a literal answer to ''What is the mode of inheritance?'' Genetic counseling is a short term process of exploring the role that genetic information plays in people's lives. It may include grief counseling, decision making, exploring health beliefs, counseling within a cultural perspective, problem solving, or any variety of short term interventions. Genetic conditions provoke strong emotional reactions, and addressing the informational aspects at the exclusion of their psychosocial implications may fall short of addressing clients' needs.

The second assumption, which has been expressed in many descriptions and discussions about genetic counseling, is that clients understand the risk information they receive and retain it for their own use. Research from the 1970s has shown that only a small percentage of clients retain accurate risk figures.[10,11] Risk information is interpreted in the context of idiosyncratic or cultural hopes, fears, beliefs, and expectations. Although clients may request genetic risk information, they give it meaning in vastly different ways.[12] The focus of genetic counseling is to work with risk perception, i.e., understand the meaning that the client gives the information. This meaning, along with individual personality traits, is likely to have the most profound impact on coping with a risk in the family and on decision making about genetic testing or childbearing.

Third, there is a misunderstanding that clients base decisions solely on risk information. Research has suggested that risk perception may not be influenced much by the provision of either genetics education or the combination of education and counseling.[13] Risks may be assimilated over an extended period and become incorporated into a person's expectations and self-concept.[14] Decisions seem to be made based on a complex interplay of ideas and feelings. Many decisions may not appear rational to another individual but may feel consistent or rational to the one faced with the decision. Thus, genetic counselors should strive not to harbor preconceived notions about whether certain outcomes or decisions are ''right'' or rational.[15] Counselors should strive to assist clients in making autonomous decisions that they can factor into their lives with a certain degree of acceptance and satisfaction.

One of the challenges in providing genetics information includes providing a thorough, accurate, and balanced presentation of the facts. Counselors have personal and professional biases that influence the provision of information. Although genetic counselors are trained to be sensitive to these biases and may do a responsible job of presenting information, it is still difficult to achieve a complete balance.

Much of the information provided is abstract to clients and packaged in difficult concepts, such as probabilities or likelihood. There are many aspects of genetic counseling that are difficult to explain in concrete terms. Clients may be overloaded with more factual information than they can use or than has meaning for them. It becomes difficult for providers who value informed decision making to recognize that leaving out some of the details may help clients to process what they hear into something useable. For instance, it is simplest to explain that we have two copies of each of our genes and that we get one from our mother and one from our father. It may not be necessary to complicate the discussion with details of cellular biology. Another educational challenge is the finding that most clients lack a scientific background, in particular in biology and genetics. It may be difficult for them to conceive of genes or understand how they can be examined through a blood sample. Visual tools can aid in explanation but do not guarantee understanding.

Perhaps the most significant barrier to transmitting factual information is the emotional factor. The context of the information directly affects comprehension. Has a child been diagnosed with a fatal condition? Has the condition existed in the family for generations, or is this the first diagnosis? Did the client seek the information, or was he or she referred by a concerned professional? Issues such as personal vulnerability, the burden of the condition, shame or guilt issues, and the ambiguity of the situation all play a role in the relationship between the counselor and the client and in the outcome of the counseling. Personality traits of the client will affect the meaning placed on the information and decisions made. The counselor's agenda for the interaction must reflect or at least compliment the client's agenda if an effective exchange is to transpire. Further research is needed to assess the effectiveness of genetic counseling in meeting the needs of clients and what strategies should be employed.[16]

Increasingly, genetic counselors and genetic nurses have become subspecialized. One of the newest areas of practice specialization is oncology genetics;

an increasing but still limited number of genetic counselors, physicians, and nurses are acquiring this expertise.[17]

Familial Cancer Risk Counseling

Already the applications of new genetic and molecular technologies are being observed in every phase of cancer care, including prevention, screening, diagnosis, prognosis, treatment, relapse detection, and even gene therapy. Within this spectrum, cancer susceptibility holds a special place because it implicates the entire family and not only the individual.

Familial cancer risk counseling (FCRC) is a communication process between a health care professional and an individual concerning the occurrence, or risk of occurrence, of cancer in the individual's family.[18] This is distinguished from life-style counseling and health education in that FCRC is much more comprehensive in scope, includes a strong emphasis on analysis of genetic and other risk factors, and is customized to the individual rather than being a general educational activity. Ideally, FCRC addresses genetic risk, medical management, and psychosocial issues as needed by participants.[17–26]

Increasingly, FCRC programs are being established in comprehensive cancer centers, oncology offices, genetics clinics, breast centers, and gastroenterology clinics. There are good reasons for starting such programs. Initially, the program may be a response to repeated requests from persons with concerns about cancer risk that may affect either themselves or their relatives. It can also broaden traditional oncology practice by expanding the focus on the individual with cancer to a wider concern for the entire family.

Operation of an FCRC Program

Before beginning an FCRC program, it is important to consider what the goals of such a program will be and how they will fit with the mission of the organization and national cancer control objectives. Some potential goals include increasing quality of care for oncology patients and their families and providing information to facilitate medical and life-style decisions that may eventually reduce cancer morbidity and mortality.

To accomplish whatever goals are set, the FCRC program leadership will need to face several significant organizational decisions. For example, will the FCRC focus on a particular cancer type or be broad-based enough to address all familial cancers? How will the program handle medical surveillance and management of risks for more than one type of cancer known to be present in most hereditary cancer syndromes? Should an FCRC program enhance already existing high priority services or begin de novo? How will knowledge of the genetic status of patients be incorporated into treatment planning? Will the entire range of FCRC services be provided on-site at each institution, or will different levels of evaluation, counseling, and testing be more regionally centralized? What resource-conserving strategies can be employed to minimize program expenses, e.g., sharing staff and resources among several departments at the same institution, using outside consultants, forming regional collaborations, or using interactive computers or videos for transmission of information? How will the FCRC program be synchronized with the activities and priorities of other cancer control organizations, such as the American Cancer Society and the National Cancer Institute?

FCRC Indications and Referrals

Persons seeking FCRC may or may not be patients in the health care system. Although some people requesting FCRC may have had cancer, many are not ill and do not wish to be called ''patients.'' They are sometimes referred to as ''consultands,'' ''participants,'' or ''counselees.''

Indications for referral are either generic or specific to particular syndromes. Generic indications for FCRC are cancer in two or more relatives, bilateral cancer, early-onset cancer, multiple primary tumors, and characteristic combinations of cancers. Specific indications may depend on the syndrome, e.g., breast and ovarian carcinoma for a BRCA1 testing program; breast carcinoma and a variety of other cancers for BRCA2; breast and thyroid tumors for Cowden's disease; breast, brain, and lung cancers, leukemia, sarcoma, and adrenocortical cancers due to p53 mutations associated with Li-Fraumeni cancer syndrome; and so forth.

All medical practitioners should now be screening oncology patients for at least preliminary indications of possible familial clustering of cancer. The emphasis should be on identifying families that have already manifested a genetic predisposition to cancer. Each person entering the oncology clinic should have a minimal history of all types of cancers among both paternal and maternal relatives. When selecting a screening tool, the practitioner should again be clear that he or she is covering all differential diagnoses of hereditary cancer syndromes that include the disease in the proband.

In addition, there may be times when individuals seek out FCRC on their own, and the program should be flexible in accommodating their needs and wishes as well. For example, sometimes a person seeks risk counseling when a relative or close friend has recently been diagnosed with cancer or a cancer recurrence.

Adult survivors of pediatric cancer syndromes, such as familial adenomatous polyposis, Wilms' tumor, or retinoblastoma, seek cancer risk counseling when they reach adulthood, for purposes of medical, financial, or reproductive planning. Some couples may inquire about the availability of prenatal diagnosis of cancer susceptibility, although this is not generally indicated or advised for adult onset disorders. Other participants may be motivated by media features or announcements of promising technical discoveries.

The FCRC Clinic Site

The clinical office for an FCRC ideally should be quiet, private, and comfortable, to accommodate lengthy discussions with multiple family members who may choose to attend together. The typical examination room may not be suitable if it is a reminder of prior medical visits and evokes unpleasant associations. FCRC programs may be situated physically in high risk clinics, prevention programs, breast screening and diagnostic centers, medical offices, genetic centers, research institutions, or freestanding facilities.

FCRC Personnel

Optimally, cancer risk counseling is provided by a multidiscipline team of professionals with some combination of oncology, genetics, and counseling backgrounds. Success is fostered by having an adequately trained and supported staff. The risk counselor should be a Master's level genetic counselor, an advanced practice nurse, or another health care professional with equivalent or greater training and professional certification or licensure. Even those holding professional degrees must be specifically trained in and dedicated to FCRC service. This means having had intensive initial training in FCRC and being involved in ongoing education and professional growth opportunities. The National Society of Genetic Counselors has formed a special interest group to address the educational, research, clinical, and networking needs of genetic counselors specializing in cancer genetics. Some oncology nurses subspecialize in genetics, and there is growing appreciation of the need for more nurses trained in cancer genetics.[27–29] There are several sources for locating cancer genetics professionals. Counselors specializing in cancer genetics can be reached at the National Society of Genetic Counselors in Wallingford, PA. Oncology nurses with a focus on genetics can be contacted at the Oncology Nursing Society, Pittsburgh, PA. Nurses with more general genetics training and experience can be contacted at the International Society of Nurses in Genetics in Buffalo, NY. Medical geneticists can be reached at the American Society of Human Genetics and at the American College of Medial Genetics in Rockville, MD. A directory of cancer genetic counselors is also available from the American Cancer Society, Atlanta, GA. Another listing of FCRC providers is now available through the National Cancer Institute's Cancer Information Service, which can be reached on the Internet [URL: http://cancernet.nci.nih.gov] or at 1-800-4CANCER.[30] A genetic counselor or nurse is most often part of a team that includes a medical oncologist and other specialists, such as a radiologist, a pathologist, and a psychologist. At a cancer center, this team may work together to provide a comprehensive service to clients who have concerns about their cancer risk.

Financial and Data Management

Record systems must be established for dealing with FCRC programs. The programs that grow out of existing cancer registries may need to establish how research and clinical records will be kept separate for security reasons but coded and linked for purposes of pedigree interpretation, genetic counseling, and genetic testing. Even programs that are purely clinical should establish minimal registry components so that specific subsets of consultands can be accessed as new genes are discovered and medical applications can be developed, altered, or made available.

Billing and reimbursement for genetic counseling services are in a state of flux. There are no CPT billing codes appropriate at this time for the amount of work and the level of specialized care required to manage families with hereditary cancers. A national survey of genetic counselors providing FCRC is being undertaken to determine billing for services and the level of reimbursement for these services (Barbara Bernhardt, Johns Hopkins University School of Medicine, personal communication, 1996).

A further difficulty with billing for genetic counseling and testing for cancer susceptibility arises from the organization of the health care and insurance industries in the U.S. Families, fearing insurance and employment discrimination, are reluctant to notify insurance companies of their participation in FCRC programs and often prefer to pay out-of-pocket for these services, if they have the means to do so, or forgo participation altogether. When families do choose to participate, it is important to track revenues generated by multiple family members who are receiving multiple spin-off services, so that the program will reflect both indirect and direct revenues for all family members affected by FCRC.

Cost-Effectiveness of FCRC

It is now common to justify medical programs by evaluating their economic impact on the institution or organization with which they are connected. There are

two types of economic assessment of the value of a medical intervention: 1) cost-benefit analysis, in which both the costs and the outcomes are expressed in monetary terms, such that dollar amounts have to be assigned to individual lives; and 2) cost-effectiveness analysis, in which the net costs of providing the service and the outcomes obtained are measured in standard units, such as dollars per life-year gained.[31] This cost-effectiveness ratio takes into account the possibility of improved outcomes that are deemed worthy of the use of more resources. It also allows for comparison of different interventions given a fixed amount of resources.

The cost-effectiveness of FCRC and testing programs have not yet been established, although there are some early indications that genetic testing and subsequent alteration of medical screening, diagnosis, and treatment procedures may be cost-effective for von Hippel-Lindau syndrome (VHL) and hereditary nonpolyposis colorectal cancer (HNPCC). Green evaluated a Newfoundland VHL overall screening program, comparing medical and psychosocial outcomes and costs for management of participants with VHL in screened and unscreened cohorts.[32] In the screened group, early deaths, disabilities and anxiety were reduced, and understanding of VHL was increased. When costs of deaths and disabilities were included, costs for screening and treatment of the screened group were less than costs for management of participants with VHL without screening. When molecular testing to identify gene carriers was included in the screening program, costs were minimized and reproductive options maximized.

Vasen et al., from the Dutch HNPCC Collaborative Group, showed that colonoscopy surveillance of mutation carriers at 2- to 3-year intervals would lead to an increase in life expectancy of approximately 10 years, and that the costs of surveillance were assumed to be ultimately less than the costs of ''no surveillance.''[33] However, another analysis showed that favorable levels of cost-effectiveness for genetic screening for a given population are achieved only when the most favorable assumptions are made about HNPCC prevalence and the cost and effectiveness of screening and prevention measures.[34] Thus, cost-effectiveness will need to be established independently for different populations.

These types of studies, which factor in changes in surveillance and treatment costs along with the costs of counseling and testing, need to be replicated, expanded, and extended to clients with other hereditary conditions. This will help demonstrate the value of conjoining risk counseling and testing with attention to appropriate medical and psychologic management of persons at various levels of genetic risk.

Despite the attractiveness of these types of studies in the current health care milieu, we must carefully consider ethical dilemmas that may arise, e.g., a conflict between patient autonomy and cost-effectiveness. For example, if FCRC or genetic testing is found to be cost-effective for specific populations, should we then advocate or even require that certain people be tested? Will certain services be withheld or payment offered based on testing outcomes? Will this exert unfair coercion to receive genetic services?

Components of FCRC Programs

A number of descriptions of the activities subsumed under FCRC have been published.[17,22,24,35–38] The main activities include the compilation of detailed family, medical, and life-style histories; documentation of cancer-related diagnoses; pedigree construction and analysis; risk assessment and counseling; susceptibility testing, when appropriate; discussion of options for medical management of cancer risk; and provision of reassurance and support as needed. A summary of the possible interrelationships of all of these activities is provided elsewhere and summarized in Figure 1.[17]

Triage in FCRC

For persons who have a positive family history of cancer, the first step is to make a very brief assessment of the situation before premature reassurance or launching into comprehensive FCRC. People may seek FCRC for a variety of reasons. The first level of triage is to determine the concerns of the individual. These may be genetic, medical, psychologic, or a combination thereof. For example, some women may be concerned about having a relative with breast carcinoma but have not mentioned to the provider their worry about a current breast lump or nipple discharge. Obviously, a medical evaluation would take precedence over genetic risk assessment in such a case; however, the risk assessment may also add information to the diagnostic workup. Other people may be experiencing symptoms of psychologic distress due to worries about their children being diagnosed with a cancer that they may assume is hereditary or due to acute or chronic grieving over loved ones lost to cancer. The initial contact with the person seeking FCRC must always begin with a sensitive triage interview to determine whether there are pressing medical or psychologic needs that should be addressed before issues of genetic risk.

Family History in FCRC

Although brief information about the family history may be obtained during the initial screening, more

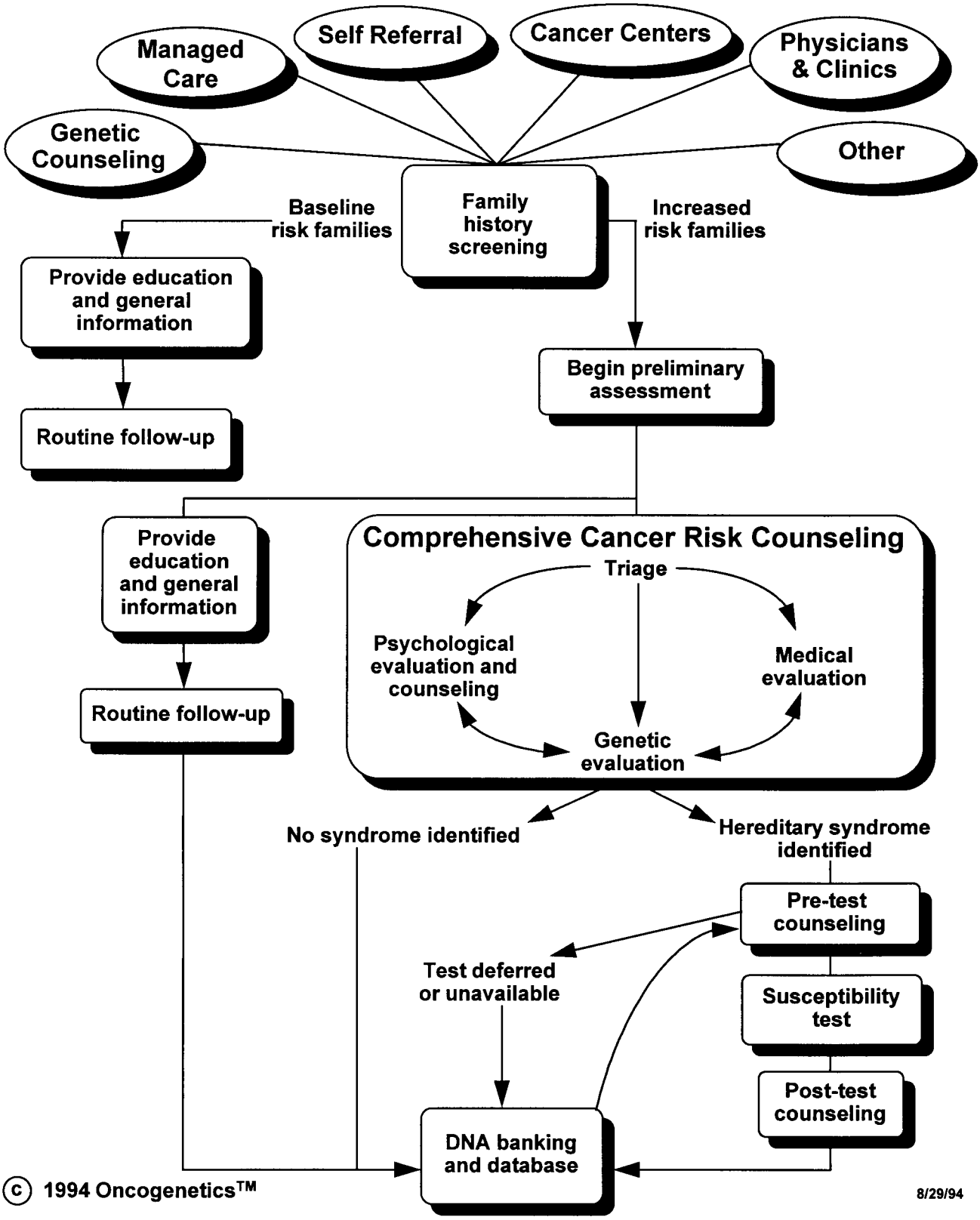

FIGURE 1. Protocol for cancer risk assessment and counseling is shown.

detailed cancer history is called for in the comprehensive genetic evaluation of familial clusters of cancer. The practitioner should make the history relevant to the present illness, beginning by evaluating the health of the consultand in his or her office and working outward from the nuclear family, extending to grandparents, aunts and uncles, and beyond as necessary. Recording racial and ethnic background in all cases is essential, as certain mutations are found preferentially in certain populations, and inquiries should also be made about possible consanguinity that might point to an autosomal recessive condition. It is important to include and document all cancers, and in so doing obtain reports on the type, site, stage, bilateral status, and age at onset for all affected individuals.[22] This is especially helpful in distinguishing multiple primaries from recurrences or metastases and establishing syndrome diagnoses that are based largely on family history. Unaffected relatives should also be included, because the proportion of affected to unaffected persons within a family is important.

The information collected is generally converted to a family pedigree at some point. The genetic pedigree is a shorthand, graphic representation of the family's medical history. Recommendations for standardized human pedigree nomenclature have been published recently.[39] The genetic counselor can use the pedigree to see conveniently and quickly the number of affected individuals, how many generations are affected, and the pattern and distribution of cancers on both sides of a family. This greatly aids in establishing hereditary syndrome diagnoses.

Familial Cancer Risk Assessment

Cancer risk assessment refers to the process of quantifying the statistical probability of an individual's developing cancer due to the presence of variables such as family history, environmental exposures, life-style, and chance. An estimate of cancer risk is often offered in comparison to the ''baseline'' risk of cancer for the general population.

Hoskins et al.[40] presented a guide for primary care clinicians to use in evaluating families for inherited breast carcinoma risk. The guide separates the risk assessment and counseling of moderate risk families (with one or two affected relatives) from high risk families (those most likely to have a hereditary syndrome). This is useful because it allows the counselor to approach risk assessment differently depending on whether or not a hereditary condition is suspected. In many cases, the distinction between low, moderate, and high risk is not clear, even after extensive family pedigree. In such cases, the counselor may give the consultand both empiric and Mendelian risk assessments, with the explanation that clear-cut estimates are impossible at that time.

The majority of patients seen in a familial cancer clinic are likely to have a moderate cancer risk.[37] There are several methods of assessing moderate breast carcinoma risk. These have been summarized by Hoskins et al.[40] and Offit and Brown.[41] The essence of the process is to use available epidemiologic data to estimate relative risk or cumulative lifetime risk for developing cancer. The Gail model, for example, consists of a multifactorial model of breast carcinoma and includes risk factors such as current age, age at menarche, age at the birth of the first child, number of biopsies, and number of first-degree maternal relatives affected.[42] The Claus model, derived from the Cancer and Steroid Hormone study conducted by the Center for Disease Control, offers tabular risk data for cumulative risk estimates for defined age intervals. This model can be readily applied to clinical counseling situations.[43]

The main advantage of these systems of risk modeling is that some estimate of risk can be given to clients who do not fit recognized susceptibility syndromes. The disadvantage is that the group from which the data is drawn is genetically heterogeneous. None of these models are reliable at the risk extremes, e.g., for a truly high risk woman carrying a mutation of a cancer susceptibility gene. If her history represents an unrecognized susceptibility syndrome, she may also be at risk for other cancers not accounted for in the model. A recent comparison of the Gail and Claus models showed that the two methods may result in substantially different estimates of breast carcinoma risk for some patients.[44] This serves to emphasize that the numeric figures derived from these models are imprecise estimates at best when applied to the individual.

Although it may be easy to use a computer printout or risk table to generate a risk estimate, simply supplying this information is insufficient to relieve the worries of clients or change their behavior. It has been demonstrated that ''efforts to counsel women about their breast cancer risks are not likely to be effective unless their breast cancer anxieties are also addressed.''[45] Individuals with moderate genetic risk for cancer may be just as anxious about this perceived risk as people who belong to families with proven hereditary syndromes. A person at moderately increased risk may also be very interested in discussing hormone replacement, diet, exercise, complementary medicine, or other ways of modifying or coping with perceived risk.[35] Therefore, as in the hereditary cases, sufficient time and attention to medical, psychologic, and social needs should be given during the risk counseling interaction.

The same empirical cancer risk counseling approaches can be applied in counseling that addresses familial colorectal carcinoma[46–49] and familial ovarian carcinoma.[50–54] Empirical data for other potentially familial cancers is currently not widely available to provide adequate cancer risk assessment.

''High risk'' families with known hereditary cancer susceptibility syndromes can be ascertained primarily by characteristic family histories. There are several benefits of making such a diagnosis: 1) the individual cancer risks will be signficantly higher than in the moderately increased risk group; 2) the risks may apply to several types of cancer and not only the most prevalent one; 3) genetic susceptibility testing may be available to allow first-degree relatives to know whether or not they have inherited a susceptibility gene mutation; and 4) early identification of those ''at risk'' may allow for possibilities of prevention, early detection, or early treatment that could forestall permanent disability caused by syndromes such as retinoblastoma, multiple endocrine neoplasia, and VHL.

Familial Cancer Risk Notification

Once risk has been assessed, it needs to be communicated in an understandable way to counselees. Transmission and interpretation of risk information is challenging because of a variety of complexities already mentioned above. It is important to elicit a person's understanding of his or her risk and the beliefs underlying this understanding before risk information is conveyed. Indeed, some persons may not want to be provided with specific risk information at a given time.[55] For those who desire risk information, it helps to provide a cognitive framework by giving a significant amount of background information about cancer, principles of heredity, and laws of probability.[36]

It is essential that risk information be communicated in a way that is meaningful to the participant. The chances of being understood are often increased if the counselor uses a variety of means, such as giving information in the forms of fractions and percentages and using both visual and verbal messages. It is also customary to discuss the chances that the individual will not inherit a particular mutation, e.g., a 25% risk of inheriting a mutation means a 75% chance of not inheriting the mutation.

The main recommendation of a recent report to the National Cancer Institute of Canada summarizes the appropriate stance regarding communicating risk in the context of familial cancer:

> The disclosure of risk estimates for cancer should be tailored to individuals' affective states and information processing preference, and should consider pre-existing perceptions of risk. The communication of risk estimates must reflect uncertainty and potential for error. All individuals receiving risk information, regardless of results, should be informed about early detection health practices. Finally, those individuals who receive low risk estimates should be informed about their continued risk for sporadic cancers.[56]

Genetic Susceptibility Testing for Hereditary Cancer

Genetic susceptibility tests provide a very specialized type of genetic information; as such, they differ from other types of medical tests. Results have implications for extended families. Test results for most susceptibility syndromes are probabilistic and not a definite indication that the person will develop a particular type of cancer by a certain time. For these and other reasons, it is essential to provide adequate pretest and posttest genetic counseling as well as longitudinal follow-up.

Pretest Genetic Education and Counseling

It is often the case that, outside of genetic counseling, only minimal information is given to the patient about medical testing being performed, unless there is an abnormal result. Genetic testing differs in that it may not be medically indicated in many instances. In most circumstances, a thorough informed consent discussion is held to help the client make an autonomous decision about whether or not to undergo testing. A description of genetic counseling for BRCA1 susceptibility testing for inherited breast and ovarian carcinoma has been suggested by Biesecker et al. and can be applied to other inherited cancer syndromes as well.[57] This approach places a strong emphasis on the importance of pretest counseling, the multidiscipline team approach to management of genetic risk, and the necessity of follow-up for family members who are tested.

Pretest education and counseling is a process that takes place between providers and counselees, in which sufficient information for informed consent or informed refusal is provided within a supportive context. The objective is to help counselees make difficult decisions about whether or not to be tested. Geller and other members of the Task Force on Informed Consent of the Cancer Genetics Studies Consortium recommend that ''informed consent be an ongoing process and that medical professionals and participants become partners in decision making.''[58] The information given to clients during this process generally includes a description of test procedures, specificity and sensitivity, and the benefits, risks, and limitations of testing. Basic elements of informed consent for germline DNA testing for cancer susceptibility derived

TABLE 1
Informed Consent (ASCO)

- Test specifics
- Possibility that the test will be uninformative
- Implications of each result (positive, negative, or inconclusive)
- Options for risk estimation without the test
- Technical accuracy
- Fees for counseling or testing
- Risk for children
- Possible psychologic distress
- Insurer or employer discrimination
- Confidentiality and privacy
- Medical surveillance options and limitations

ASCO: American Society of Clinical Oncology.

from several sources are summarized in Table 1.[9,22,59] Perhaps it is most important that counselees understand the familial nature of testing; the role of probability in cancer prediction; the lack of information provided by a negative test result; the absence of long term follow-up data on prevention and medical surveillance recommendations for some cancers; and the potential risk for loss of health insurance, life insurance, or employment resulting from the disclosure of genetic test results.[17,60]

Pretest counseling is often a time to untangle the confusions and misunderstandings that people may have about genetic risk. Part of this clarification process involves distinguishing between several categories of risk that the person faces. These different probabilities include 1) the chance that alterations of a given gene explain the occurrences of cancer in the family; 2) the chance that a particular member of the family has inherited this mutation; 3) the probability of developing any cancer, given the presence or absence of this mutation; 4) the chances of developing specific cancers; and 5) the chances that a cancer might develop by the time a particular person is a given age. For example, is the breast carcinoma observed in a particular family due to BRCA1, BRCA2, p53, CD, ATM, or another breast carcinoma susceptibility gene? Once the correct gene has been identified, a priori Mendelian risk estimates can be offered. For a dominant mutation, an individual has a 50% chance of inheriting the mutant gene from an affected parent and a 50% chance of inheriting the functioning gene. However, having a germline mutation is not the same as having cancer. Thus, there is a separate probability that the person bearing a germline mutation will actually develop cancer. This is based on the penetrance estimate of the genetic mutation and on other factors, such as modifying genes or exposure to environmental insults that may affect expression of the cancer. Thus, we could say that virtually 100% of persons with a certain germline RET mutation will eventually develop thyroid carcinoma. For many syndromes, there may be different probabilities of developing different cancers. For example, for women in high risk families carrying BRCA1 mutations, there is an 80–90% risk of developing breast carcinoma, a chance of approximately 60% of developing a second breast carcinoma, a chance of approximately 40–60% of developing ovarian carcinoma, possibly an elevated risk of colon carcinoma for female mutation carriers, and possibly an elevated risk of both colon and prostate carcinoma for male mutation carriers.[61] In contrast to these high penetrance figures, the cancer risk was substantially lower in the 120 out of 5318 volunteer Jewish subjects in a recent community based study who were found to carry one of three common BRCA1 or BRCA2 mutations.[62] These data suggest that in this population where there is not a strong family history of cancer, the risks may be significantly lower and it is not appropriate to use the above data from high risk families to counsel individuals without a strong family history. Finally, ages at the time of cancer onset vary widely, but there are estimates of the proportions of those carrying mutations who will be affected by a certain age, and these estimates are sometimes modified by factors such as gender. For example, in one recent study of persons carrying p53 mutations in families with Li-Fraumeni cancer syndrome, Bonaiti-Pellie found that by age 16 years, 45% of boys and 29% of girls had developed cancer, whereas by age 45 years, 52% of males and 85% of females had developed cancer.[63]

Reviewing the medical and genetic facts does not constitute adequate provision of information for informed consent. In the context of genetic counseling, exploring the meaning of the information is equally important. Counseling generally includes exploration of the implications of all results that may be positive, negative, or inconclusive. Sometimes it is possible to discern whether the person expects his or her result to be positive or negative. Participants often have preconceived notions about their results.[64] These may influence their reactions at the time of risk notification.[15]

Test Result Notification

An individual consultation, during which the person being informed of his or her result may or may not be accompanied by a support person, is generally provided for conveying test results. It is important to allow for privacy and adequate time for processing the information. The session should be dedicated to dealing with genetic, medical, psychologic, social, and economic implications of test results. Testing implications

will differ significantly from syndrome to syndrome as well as from person to person. Thus the provider should be familiar with the latest information on the gene in question as well as with the concerns of the individual testing participant.

An individual who has just learned that his or her cancer risk has substantially increased or decreased based on test results may have strong emotional reactions. Addressing the psychologic reactions to test results may begin at the time of risk notification and is likely to be ongoing. An individual may respond with shock, relief, anxiety, depression, fear, confusion, grief, loss, anger, shame, guilt, or worry about other family members. Strong reactions may occur even when test results are negative.[15]

Test Follow-Up

It is still difficult to predict who may have long term struggles in adjusting to results and who will adjust adequately over time. Those who receive negative results may be less motivated to return for long term follow-up, but experience with other genetic conditions has shown that 1 year after test notification, they can have rates of psychologic distress comparable to those of persons with positive results.[15] Thus, the provider should make every effort to maintain some long term contact with all tested individuals.

There will be many individuals in the risk counseling program who do not meet criteria for genetic testing, or choose to decline testing or defer a decision until a later date. It is important to encourage regular contact with these individuals so that family records can be updated and any new issues that may emerge can be assessed.

CONCLUSIONS

It is worthwhile for providers specializing in oncology and genetics to begin to characterize their patient population with respect to cancer risk and to offer FCRC when there are indications that risk may be elevated above baseline. FCRC is a comprehensive service that may help address concerns about cancer risk even in the absence of a hereditary cancer susceptibility syndrome. Genetic susceptibility testing for cancer is becoming available to help define genetic risk for a variety of types of hereditary cancers, but it should be undertaken only in the context of genetics education and counseling and ideally within a comprehensive cancer risk assessment program.

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